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Effectiveness of insulin pump use in controlling blood glucose in type 1 diabetes mellitus patients

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Effectiveness of Insulin Pump Use in Controlling Blood Glucose in Type 1 Diabetes Mellitus Patients

by

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ABSTRACT

Glycemic control for type 1 diabetes mellitus (Type 1 DM) patients is achieved by using insulin through multiple daily insulin injections (MDI) or by continuous subcutaneous insulin infusion (CSII). This study evaluated the effectiveness of CSII in controlling blood glucose in adult type 1 DM patients. A retrospective comparison of two groups of type 1 DM patients was conducted. One group received MDI therapy and the other received CSII therapy. Parameters compared included HgA1C, fasting blood glucose concentrations, total episodes of hypoglycemia, severe and nocturnal hypoglycemia, and diabetic ketoacidosis (DKA). Results indicated a significant decrease in HgA1C in CSII patients at 3 and 6 months, a significant decrease in fasting blood glucose at 6 months, and a significant decline in the total number of hypoglycemic and nocturnal hypoglycemic events in 6 months. CSII therapy was more effective than MDI in regulating diabetes in type 1 DM patients.
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CHAPTER 1: INTRODUCTION AND BACKGROUND

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia. It is associated with abnormalities in carbohydrate, fat, and protein metabolism that result from defects in insulin secretion, insulin action (sensitivity), or both (Gardner & Shoback, 2007). The two major classifications of diabetes mellitus are type 1 DM (insulin deficiency) and type 2 DM (combined insulin resistance and relative deficiency in insulin secretion; Gardner & Shoback, 2007).

Type 1 Diabetes Mellitus (Type 1 DM) results from an autoimmune destruction of the pancreatic beta cells (Gardner & Shoback, 2007). This form of diabetes usually occurs in children and adolescents. However, it can occur at any age. A rapid rate of Beta-cell destruction is evident in younger individuals and results in the development of diabetic ketoacidosis. Acute insulin deficiency in these younger patients leads to hyperglycemia, ketonemia, low arterial blood PH, low plasma bicarbonate, and high anion gap. Children and adolescents with hyperglycemia exhibit symptoms of polydipsia, polyuria, polyphagia, weight loss, and, in severe cases, ketoacidosis and coma (Fonseca, 2006). On the other hand, adults often maintain sufficient insulin secretion, which hinders the appearance of diabetic ketoacidosis for many years (Gardner & Shoback, 2007). For this reason, some of these patients might be falsely diagnosed as type 2 diabetics (Fonseca, 2006). About 5% to 10% of adult patients who are diagnosed with type 2 diabetes actually have a progressive form of type 1 DM (Atkinson & Eisenbarth, 2001). This is often referred to as Latent Autoimmune Diabetes in Adults (LADA; Gardner & Shoback, 2007).
It is difficult to determine the exact cause for type 1 DM. However, genetic factors are known to contribute to the susceptibility of developing the disease (Winter, Harris, & Schatz, 2002). Relatives of patients with type 1 diabetes have a 15- to 20-fold increased risk of developing the disease compared with the general population (Winter et al., 2002). Even though more than twenty genes have been found to influence the susceptibility to type 1 DM, the human leukocyte antigen gene complex (HLA) located on the short arm of chromosome 6 was found to have the strongest influence on the susceptibility to the disease (Winter et al., 2002). To check for the prediction for developing type 1 DM in patients, it is advisable to check for the existence of one or more auto-antibodies known to destruct the pancreatic beta cells causing the disease (Atkinson & Eisenbarth, 2001; Winter et al., 2002). These auto-antibodies include islet cell auto-antibodies (ICA), insulin auto-antibodies (IAA), and glutamic acid decarboxylase autoantibodies (GADA; Atkinson & Eisenbarth, 2001; Winter et al., 2002). The importance of testing for the existence of the previous auto-antibodies is related to the fact that more than 90% of patients with type 1 diabetes have one or more of these autoantibodies (Winter et al., 2002). Measuring these antibodies can be helpful in the diagnosis of type 1 DM to differentiate from other types of diabetes and to predict individuals who are at high risk of developing type 1 DM (Winter et al., 2002). Even though a strong genetic predisposition to type 1 DM exists, almost 90% of the newly diagnosed cases of type I DM occur without a family history of the disease (Fonseca, 2006; Atkinson & Eisenbarth, 2001; Winter et al., 2002).

On the other hand, type 2 Diabetes Mellitus (DM) results from a combination of insulin resistance and beta cell dysfunction (Fonseca, 2006). Type 2 DM is part of the metabolic syndrome, which includes vascular inflammation, endothelial dysfunction, hypertension, dyslipidemia, central obesity, and a hypercoagulable state (Fonseca, 2006; Dandona, Aljada,
Chaudhuri, & Bandyopadhyay, 2003). Insulin resistance with type 2 DM is a condition of decreased insulin sensitivity in which insulin action to lower blood glucose level is decreased (Pirola, Jonhnston, Van Obberghen, 2004). Insulin resistance is manifested in many tissues including the liver, the muscle, and adipose tissue (Pirola et al., 2004). Insulin resistance hinders the glucose uptake by previous insulin sensitive tissues and increases the hepatic glucose output leading to hyperglycemia (Pirola et al., 2004). Increased hepatic glucose output contributes to increased fasting glucose levels. On the other hand, decreased peripheral glucose usage leads to postprandial hyperglycemia (Pirola et al., 2004). Furthermore, patients with type 2 DM exhibit a variable degree of beta cell dysfunction (Pirola et al., 2004; Henry, 2003). Depending on the degree of beta cell dysfunction, a combination of oral medications or/and insulin regimens are used to regulate blood glucose levels (Henry, 2003).

The goal of diabetes treatments for either type 1 or type 2 DM is to normalize blood glucose levels (Fonseca, 2006). Patients with type 1 or type 2 DM with uncontrolled blood glucose levels exhibit acute and chronic complications (Fonseca, 2006). The acute diabetic complications include hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS; Fonseca, 2006).

Hypoglycemia is demonstrated by blood glucose levels less than 70 mg/dl (Fonseca, 2006). As blood glucose levels fall below 70mg/dl in non-diabetic persons, the counter regulatory responses to low blood sugar levels play a significant role in defending against the occurrence of hypoglycemia by increasing blood glucose levels (Fonseca, 2006; Davis, Mann, Galassetti, Neill, Ertl, & Costa, 2000). The counter regulatory responses to hypoglycemia include stimulation of autonomic and neuroendocrine hormonal responses, which leads to the secretion of catecholamines, including norepinephrine and epinephrine (Fonseca, 2006).
Norepinephrine is secreted from the central nervous system, and epinephrine is secreted from the adrenal gland (Davis et al., 2000). The secretion of both hormones leads to an increase in blood glucose levels (Fonseca, 2006; Davis et al., 2000). Other counter regulatory responses include increased glucagon secretion from the alpha-pancreatic cells and the decrease in insulin secretion from the pancreatic beta cells (Fonseca, 2006). The catecholamines, glucagon, and insulin responses to hypoglycemia are considered the first neurohormonal responses that contribute to restoring the normal glucose levels (euglycemia; Davis et al., 2000). This restoration is achieved by increasing glucose production by the liver through glycogenolysis and gluconeogenesis and decreasing glucose uptake by insulin sensitive tissues (Davis et al., 2000). Thus, a normal glucose delivery to the brain is sustained (Davis et al., 2000). Increased catecholamines, glucagon, and decreased insulin responses to hypoglycemia lead to lipolysis and skeletal muscle glycogenolysis, which provides the necessary amino acids to the liver to be used for gluconeogenesis (Fonseca, 2006; Davis et al., 2000). If hypoglycemia lasts for more than two hours, cortisol and growth hormone secretions increase, which leads to an increase in gluconeogenesis and lipolysis and induces insulin resistance leading to euglycemia (Davis et al., 2000).

In patients with long duration of type 1 diabetes mellitus, the glucagon response to hypoglycemia is lost (Cryer, 1999). The lack of glucagon release results in an estimated 40% reduction in glucose recovery (Cryer, 1999). When glucagon responses to hypoglycemia are lost, the role of epinephrine in the counter regulation becomes critical (Cryer, 1999). However, in type 1 DM patients, prior episodes of hypoglycemia blunt the autonomic, neuroendocrine, and metabolic responses to hypoglycemia, causing more severe and frequent episodes of hypoglycemia (Cryer, 2001). This cycle of episodes of hypoglycemia attenuating counter
regulatory responses including autonomic, neuroendocrine, and metabolic is referred to as hypoglycemia associated autonomic failure (HAAF; Cryer, 2001). The autonomic failure and the presence of hypoglycemia unawareness are also evident with type 2 DM patients (Cryer, 2001). Usually, good glycemic control improves the autonomic dysfunction (Home, Lindholm, Hylleberg, Round, 1998; Gerich, 2004; Cryer, 2001).

The Diabetes Control and Complication Trial (DCCT), a study published in 1990, showed that reaching a near normal glycemic level in diabetic patients by using intensive insulin therapy prevents the development and slows the progression of diabetic complications (Diabetes Control and Complication Trial Research Group [DCCT], 1993). Furthermore, this study showed that 40% of all severe hypoglycemic episodes occur at night (Robinson, Harris, Ireland, Macdonald, & Heller, 2004). Nocturnal hypoglycemia is dangerous in that it can lead to cardiac events and arrhythmia during the night, which can have detrimental effects on patients’ lives (Robinson et al., 2004).

Hypoglycemia can occur as an acute complication in type 1 DM patients. Some of the causes of hypoglycemia include excess insulin administration, lack of appropriate food intake, and the type of the insulin treatment used (Sandoval, Aftab-Guy, & Davis, 1992; Cryer, Axelrod, Grossman, Heller, Montori, Weaquist, & Service, 2009). The type of the insulin regimen used with type 1 DM patients affects their susceptibility to hypoglycemia (Home et al., 1998; Gerich et al., 2004; Cryer et al., 2009). Regular insulin regimen may cause postprandial and pre-prandial hypoglycemia for the next meal (Home et al., 1998). This can be attributed to the time of onset, the peak, and the duration of action of the regular insulin (Home et al., 1998; Cryer et al., 2009). Regular insulin has a time of onset of 30 minutes, a peak of two hours, and duration of action of six hours in most patients (Fonseca, 2006; Home et al., 1998; Cryer et al., 2009). This regimen
may cause post-prandial hyperglycemia because the blood glucose peak after an ingested meal
does not correspond to the delayed peak of the regular insulin, which causes elevated post-
prandial blood glucose levels and pre-prandial hypoglycemia at the next meal (Home et al.,
1998; Cryer et al., 2009). To circumvent problems with elevated post-prandial glucose levels,
rapid acting insulin analogs such as Humalog, Novolog, or Apidra are used both in multiple daily
injections (MDI) and in continuous subcutaneous insulin infusion (CSII) via a pump (Home et
al., 1998; Cryer et al., 2009).

The molecular structure of Humalog, Novolog, or Apidra allows for rapid onset of action
(Fonseca, 2006; Home et al., 1998; Cryer et al., 2009). Humalog, Novolog, or Apidra exhibit an
onset of action within 5-15 minutes, peak at 90 minutes, and have a duration of action that lasts
two hours in most patients (Fonseca, 2006; Home et al., 1998). Several studies have reported that
Humalog, Novolog, or Apidra produce better glucose control and reduce the incidence of
hypoglycemia more than regular insulin (Fonseca, 2006; Home et al., 1998). The reason for that
is the better match of the timing of insulin peak and action with food absorption after meal
ingestion (Home et al., 1998). This unique property of Humalog, Novolog, or Apidra insulin
regimens allows patients to calculate their actual carbohydrate intake and match it with the
proper amount of insulin (Home et al., 1998). The action of these insulin regimens mimics the
action of a normal pancreatic insulin response in non-diabetic people and contributes to effective
blood glucose control (Fonseca, 2006). Furthermore, the fast insulin action provided by this
regimen allows better flexibility than other insulin regimens in that it allows the patient to inject
himself/herself immediately after a meal instead of injecting the insulin before the consumption
of a meal (Fonseca, 2006; Home et al., 1998). This action provides an advantage, especially
when the patient is unsure of the amount of food to be consumed in a meal (Fonseca, 2006;
Home et al., 1998). The onset and the peak of action of Novolog, Humalog, or Apidra that mimic the action of the pancreas reduce the postprandial hypoglycemia (Home et al., 1998). In addition, the previous insulin action may be useful in treating gastroparesis, which is delayed gastric emptying due to autonomic neuropathy that is manifested with nausea, vomiting, and abdominal discomfort, as well as weight loss and numerous episodes of hypoglycemia (Cryer, 2001). On the other hand, long-acting insulin, such as Neutral Protamine Hagedorne (NPH), can contribute to the increased risk of hypoglycemia (Gerich, 2004). This is attributed to its pharmacokinetic action that includes an onset of insulin action of two to four hours after the injection and a broader peak at about six to seven hours that may rapidly decline within ten to twenty hours (Gerich, 2004). For this reason, evening injections of NPH insulin can lead to nocturnal hypoglycemia due to its peak of action at about 2 a.m. when most patients exhibit high insulin sensitivity (Fonseca, 2006; Gerich, 2004). Neutral Protamine Hagedorn (NPH) action wanes in the early morning hours when patients are more insulin resistant (dawn phenomena), resulting in elevated blood sugar levels and causing hyperglycemia in the morning (Fonseca, 2006; Gerich, 2004). On the contrary, other long-acting basal insulin analogs, such as Lantus and Levemir, produce very little if any peaks due to their low solubility at the injection site, last up to 24 hours, and provide the closest to the physiologic basal insulin coverage of the long-acting insulin (Fonseca, 2006; Gerich, 2004). Due to their continuous supply of basal insulin without peaks, Lantus and Levemir insulin regimens produce less hypoglycemia than NPH insulin (Fonseca, 2006; Gerich, 2004).

Other factors that may contribute to hypoglycemia include exercise, advanced age, and ethanol consumption (Sandoval et al., 1992; Marker, Cryer, & Clutter, 1992). Exercise is considered an important component of the diabetic therapy in that it contributes to improving the
glycemic control through increasing insulin sensitivity, maintaining body weight, and reducing cardiovascular disease risk (Sandoval et al., 1992). However, exercise increases glucose uptake for several hours after the event, which may contribute to post exercise hypoglycemia, especially with an inappropriate carbohydrate consumption or increased insulin intake (Sandoval et al., 1992). Hypoglycemia related to exercise is due to increased carbohydrate requirements and depleted liver glycogen stores due to the effect of the frequency, intensity, and duration of the patient’s exercise regimen (Sandoval et al., 1992). Thus, the frequency, the intensity, and the duration of exercise are important factors to consider for preventing exercise-induced hypoglycemia (Sandoval et al., 1992). In addition, exercise contributes to hypoglycemia by blunting the counter-regulatory hormones including the autonomic and the metabolic responses in type 1 DM patients (Sandoval et al., 1992). For the previous reasons, carbohydrates should be consumed as soon as possible after prolonged exercise in order to replenish glycogen stores and prevent the occurrence of hypoglycemia (Sandoval et al., 1992). Therefore, although regular exercise is beneficial, it is considered a difficult challenge for patients with diabetes in that it enhances the insulin sensitivity and slows the counter-regulation. This effect of exercise contributes to the increased depth and frequency of hypoglycemic episodes (Sandoval et al., 1992). As a result, when exercising, type 1 DM patients need to check their blood glucose more frequently, adjust their insulin accordingly, and ingest appropriate amounts of carbohydrates when anticipating exercise (Sandoval et al., 1992). Patients’ education on the effect of exercise on blood glucose levels is thus critical in order to prevent hypoglycemia (Fonseca, 2006; Sandoval et al., 1992).

Furthermore, type 1 and type 2 DM patients with advanced age suffer from a significant increased risk for hypoglycemia due to the declining liver and renal functions (Fonseca, 2006;
Marker, Cryer, & Clutter, 1992). The decreased glucose production from the liver in type 1 and type 2 elderly patients, in addition to the decreased renal clearance of diabetic medications, especially sulfonylureas and insulin, causes increased incidence of hypoglycemia (Fonseca, 2006; Marker et al., 1992).

In addition, ethanol consumption contributes to the increased risk for hypoglycemia, most likely due to a lowered neuroendocrine counter regulatory response (Fonseca, 2006). As a result, excess ethanol consumption is not advisable because of its potential to induce hypoglycemia in type 1 DM patients (Cryer et al., 2009).

To treat mild hypoglycemia, all patients should have a rapidly available source of glucose at all times to help increase their blood glucose value to the normal range of 70 to 130 mg/dl (Cryer et al., 2009). The rule of 15 is a helpful treatment regimen for hypoglycemia. This includes consuming 15 gms of carbohydrates. These carbohydrates include rapidly absorbed forms of glucose, such as glucose gel, sugar containing soda, or glucose tablets (Cryer et al., 2009). This consumption raises blood sugar values by 15 mg/dl in 15 minutes (Cryer et al., 2009). Patients should check their blood sugar after 15 minutes of their carbohydrate consumption to determine if they reach the normal range of blood glucose values. It is important to note that patients with poor glucose control for extended periods of time feel the hypoglycemic symptoms at higher levels of blood glucose values than 70 mg/dl (Cryer et al., 2009). To treat this condition, the patient can ingest 5 gms of rapidly absorbed carbohydrate. If a patient is unconscious, an administration of 1 mg of intramuscular glucagon injection is advisable (Cryer et al., 2009).

Other acute diabetic complications include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS; Fonseca, 2006). Both disorders are characterized by
insulin deficiency, volume depletion, and acid-base abnormalities (Fonseca, 2006). Diabetes ketoacidosis (DKA) is a state of uncontrolled catabolism triggered by a relative or absolute deficiency in circulating insulin; it includes a triad of high anion gap metabolic acidosis (pH less than 7.35), hyperglycemia (blood glucose levels more than 250 mg/dl), and positive ketones in the blood or urine (Gardner & Shoback, 2007; Fonseca, 2006). Diabetes ketoacidosis is manifested with nausea, vomiting, thirst, and polyuria as well as abdominal pain and shortness of breath, and it is a dangerous diabetic complication because it may result in coma and death (Gardner & Shoback, 2007; Fonseca, 2006). Diabetes ketoacidosis is a life-threatening state with a mortality rate of 5% in diabetic patients under the age of 40 (Malone, Morrison, Pavan, & Cuthbertson, 2001). A mortality rate higher than this percentage due to DKA may be seen with type 1 DM elderly patients (Frank, 1991).

Poor compliance related to psychological reasons or to inadequate patient education is the most common cause of diabetic ketoacidosis, especially when the episodes are recurrent (Frank, 1991). In adolescents with type 1 diabetes mellitus, recurrent episodes of diabetic ketoacidosis often indicate the need for counseling to alter the patient’s behavior (Frank, 1991). Many patients who monitor their capillary blood glucose regularly ignore monitoring their urine ketone measurements, which can signal the possibility of developing diabetic ketoacidosis (DKA; Cryer et al., 2009).

On the other hand, hyperglycemic hyperosmolar state (HHS) occurs with elderly type 2 diabetes mellitus patients, which is manifested with the absence of ketosis, insulin deficiency, and impaired skeletal muscle glucose utilization (Gardner & Shoback, 2007; Fonseca, 2006). Hyperglycemic hyperosmolar state (HHS) causes hyperglycemia and diuresis contributing to water volume depletion, which can also contribute to coma and death (Gardner & Shoback,
Lower levels of counter regulatory hormones and free fatty acids are noted in patients suffering HHS (Gardner & Shoback, 2007; Fonseca, 2006).

Good control of blood glucose levels as reflected by HgA1C levels less than 6.5 can prevent or postpone chronic diabetic complications including vascular and non-vascular complications (Gardner & Shoback, 2007; DCCT, 1993; Fonseca, 2006). Although all of the known complications of diabetes can be found in both type 1 and type 2 diabetes, some are more common in one type than the other (Gardner & Shoback, 2007; DCCT, 1993; Fonseca, 2006).

The vascular complications include microvascular and macrovascular complications (Gardner & Shoback, 2007; DCCT, 1993; Fonseca, 2006). The microvascular complications are due to disease of the smallest blood vessels including capillary and pre-capillary arterioles manifested mainly by thickening of the capillary basement membrane (Gardner & Shoback, 2007; DCCT, 1993; Fonseca, 2006). These microvascular changes are caused by chronic hyperglycemia (Gardner & Shoback; 2007; DCCT, 1993; Fonseca, 2006). They are mainly manifested by retinopathy, nephropathy, and neuropathy (Gardner & Shoback, 2007; DCCT, 1993; Fonseca, 2006).

The microvascular complications involving the retina lead to diabetic retinopathy (Malone et al., 2001; Frank, 1991). Diabetic retinopathy can cause blindness in both type 1 and type 2 DM patients (Malone et al., 2001; Frank, 1991). However, the cause of blindness is different in each type of diabetic patients (Malone et al., 2001; Frank, 1991). In type 1 diabetic patients, blindness can occur as a result of severe proliferative retinopathy, vitreous hemorrhages, and retinal detachment (Malone et al., 2001; Frank, 1991). Macular edema and ischemia are the usual cause of blindness in type 2 DM patients (Malone et al., 2001; Frank, 1991). Diabetic retinopathy is a major cause of morbidity in patients with diabetes (Malone et al.,
It remains the primary cause of blindness in diabetic patients in most industrialized countries (Malone et al., 2001; Frank, 1991). For this reason, it is important to regularly screen diabetic patients for the development of retinal disease (Malone et al., 2001; Frank, 1991). Type 1 diabetes mellitus patients usually will not develop retinopathy until three to five years after the onset of the disease or three to five years after the onset of puberty (Malone et al., 2001; Frank, 1991). After 20 years of the disease, evidence of retinopathy is present in almost 100% of patients with type 1 DM and 50% to 80% of those with type 2 DM (Malone et al., 2001; Frank, 1991). The incidence of blindness in diabetics is 25 times higher than in the non-diabetics due to the high incidence of retinopathy in these patients (Malone et al., 2001; Frank, 1991). Treatment of diabetic retinopathy is primarily directed at both prevention through tight glycemic control and treatment of the already established ocular disease (Malone et al., 2001; Frank, 1991). Early detection and control of the ocular disease is essential for maintaining vision in diabetic patients (Malone et al., 2001; Frank, 1991). Intensive systemic control of the blood glucose levels is the most important preventive treatment for type 2 diabetic patients (Malone et al., 2001; Frank, 1991). Advances in the ocular detection, staging, and treatment of diabetic retinopathy in addition to systemic glucose control have greatly improved visual acuity outcomes in diabetic patients (Malone et al., 2001; Frank, 1991). Patients with type 1 diabetes should be referred to a general ophthalmologist or retinologist within five years of initial diagnosis or at the onset of puberty (Malone et al., 2001; Frank, 1991). Patients with type 2 diabetes should be referred at the time of initial diagnosis because they may manifest diabetic retinopathy at that time (Malone et al., 2001; Frank, 1991). Through appropriate follow-up of mild-to-moderate non-proliferative diabetic retinopathy, many patients can receive sight-saving treatment (Malone et al., 2001; Frank, 1991). Patients suffering from proliferative diabetic
retinopathy can be treated successfully with aggressive retinal photocoagulation and operative procedures (Malone et al., 2001; Frank, 1991). Such treatments can often stop the progression of diabetic retinopathy and prevent any further loss of visual function (Malone et al., 2001; Frank, 1991). The main emphasis of the prevention and treatment of diabetic retinopathy is the frequent follow-up of the patient by the primary care physician or endocrinologist to facilitate intensive glycemic control (Malone et al., 2001; Frank, 1991). Ophthalmic follow-up is critical to ensure the early detection of diabetic retinopathy and for treatment administration at critical stages of the disease progression (Malone et al., 2001; Frank, 1991).

Furthermore, microvascular complications involving the kidneys include diabetic nephropathy (Kidney Disease Outcome Quality Initiative, 2004; Dalla, Saller, & Bortoloso, 2004; Tobe, McFarlane, & Naimark, 2002). The natural history of diabetic nephropathy associated with type 1 diabetes is characterized by early presence of microalbuminuria with subsequent development of hypertension and declining glomerular filtration rates (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). In type 2 diabetes, hypertension and albuminuria are generally present on the initial diagnosis of the disease (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). Diabetic renal disease occurs in either type 1 or type 2 diabetics particularly in patients with poor glycemic control, elevated blood pressure, and elevated blood lipids (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). In general, patients with type 1 diabetes who have not received intensive insulin therapy and have had only fair-to-poor glycemic control have a 30 to 40% chance of having nephropathy after 20 years. On the other hand, only 15 to 20% of type 2 diabetics who do not receive intensive insulin therapy develop clinical renal disease (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe
et al., 2002). However, end-stage renal disease is much more prevalent in people with type 2 diabetes in the United States and throughout the rest of the world because of the higher number of individuals affected with type 2 diabetes than type 1 diabetes (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). Improved glycemic control and more effective therapeutic measures to correct hypertension can contribute to reduced incidence of end-stage renal disease in both types of diabetics (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). Early detection of diabetic nephropathy by screening for microalbuminuria, small amounts of urinary albumin, can predict the development of end-stage renal disease (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). Careful glycemic control may reduce both the hyperfiltration and the microalbuminuria in patients in the early stages of diabetic nephropathy (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). Antihypertensive therapy is used to decrease microalbuminuria, including ACE inhibitors and angiotensin II receptor blockers, even in the absence of hypertension (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). Progressive diabetic nephropathy consists of proteinuria of varying severity, occasionally leading to nephrotic syndrome manifested with hypoalbuminemia, edema, increased circulating LDL cholesterol, and progressive azotemia, which is a medical condition characterized by abnormally high levels of nitrogen containing compounds in the blood, such as urea and creatinine (renal failure; Fonseca, 2006; Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002). End stage renal disease (ESRD) and renal failure due to severe microvascular nephropathy is considered the major cause of death in patients with type 1 diabetes (Kidney Disease Outcome Quality Initiative, 2004; Dalla et al., 2004; Tobe et al., 2002).
Genetic predisposition plays a role in the development of microvascular diabetic complications in that some diabetic patients may never develop retinopathy or neuropathy (Fonseca, 2006).

Moreover, microvascular complications involving the nerves include diabetic neuropathy. Up to 50% of patients with type 1 and type 2 diabetes suffer from neuropathy (Shaw, Zimmet, & Gries, 2003). Diabetic neuropathy contributes to 50-75% of ulcers and limb amputations in diabetic patients (DCCT Research Group, 1995; Shaw et al., 2003). Foot ulceration is considered the major complication of neuropathy, which can cause foot gangrene and subsequent limb loss (DCCT Research Group, 1995; Shaw et al., 2003). In addition, neuropathy has an effect on the diabetics’ quality of life in that it limits many activities of the patients’ daily living (DCCT Research Group, 1995; Shaw et al., 2003).

Diabetic neuropathy includes polyneuropathy, mononeuropathy, and autonomic neuropathy (Fonseca, 2006; Shaw et al., 2003). Polyneuropathy affects numerous nerve roots and causes distal equal sensory loss in the legs, feet, and the gloves of the hands, known as stocking glove syndrome (Fonseca, 2006; Shaw et al., 2003). This sensory loss causes feelings of numbness, tingling, and sharpness, as well as burning sensations in the feet that extend towards the center of the body (Fonseca, 2006; Shaw et al., 2003). Patients may exhibit pain in their legs and feet when resting or in the evening (Fonseca, 2006; Shaw et al., 2003). As diabetic neuropathy progresses, pain lessens until it stops (Fonseca, 2006; Shaw et al., 2003). However, sensation in the legs and the feet accompanied by disappearance of the ankle reflexes are noted when pain is no longer present (Fonseca, 2006; Shaw et al., 2003).

Mononeuropathy is caused by a dysfunction of a single nerve of the cranial or peripheral nerves, which causes pain and motor weakness (Fonseca, 2006; Shaw et al., 2003; Jameson,
The third cranial nerve is usually most commonly associated with mononeuropathy and causes diplopia known as double vision (Fonseca, 2006; Jameson, 2006).

Autonomic neuropathy affects multiple body systems, including the cardiovascular, the gastrointestinal, and the genitourinary, as well as the sudomotor and the metabolic systems (Vinik, Maser, Mitchell, Freeman, 2003). It may cause erectile dysfunction, gastroparesis, and orthostatic hypotension (inaability to regulate the blood pressure when standing; Vinik et al., 2003). In addition, autonomic neuropathy contributes to diabetic diarrhea and atonic urinary bladder (absence of the ability to control bladder functions; Vinik et al., 2003). Diabetic neuropathy is found in both type 1 and type 2 diabetic patients. However, type 1 patients more commonly exhibit symptoms of severe autonomic neuropathy (Vinik et al., 2003). These symptoms include gastroparesis, diabetic diarrhea, and resting tachycardia, in addition to orthostatic hypotension (Vinik et al., 2003).

Microvascular complications as described above are common in diabetes. The occurrence of macrovascular disease, the disease of the large vessels, is also problematic in patients with diabetes. Macrovascular complications are considered the leading cause of death in type 2 diabetic patients (Kennel & McGee, 1979; Stratton, Adler, Neil, Manley, Cull, Hadden, Turner, & Holman, 2000). They include coronary artery disease (CAD), peripheral arterial disease (PVD), and cerebrovascular disease (CVA; Kennel & McGee, 1979; Stratton et al., 2000). It accounts for the increased incidence of myocardial infarction, stroke, and peripheral gangrene in diabetic patients (Klein, 1995; Kuller, Velentgas, Barzilay, Beauchamp, O’Leary, & Savage, 2000).

Diabetes has long been recognized as an independent risk factor for cardiovascular disease (Kennel & McGee, 1979; Stratton et al., 2000, Klein, 1995; Kuller et al., 2000). The
adverse influence of diabetes extends to all components of the cardiovascular system, the microvasculature and larger arteries as well as the heart and kidneys leading to frequent microvascular and macrovascular complications (Stratton et al., 2000). Coronary artery disease (CAD) remains asymptomatic in diabetic patients for several years and is often in advanced stages of development by the time it is discovered (Kuller et al., 2000). The mortality rate with diabetic patients suffering from CAD is considered higher than with non-diabetic persons once a primary event of heart disease has occurred (Kuller et al., 2000).

Furthermore, peripheral vascular disease (PVD) is a common macrovascular complication in DM patients and is due to atherosclerosis in the large arteries (Jameson, 2006). The clinical manifestations of PVD include ischemia of the lower extremities, impotence, and intestinal angina (Jameson, 2006). The incidence of foot gangrene in people with diabetes is 30 times higher than that in age-matched controls without diabetes (Jameson, 2006). The factors responsible for the development of gangrene in diabetic patients include peripheral vascular disease, small vessel disease, peripheral neuropathy with loss of both pain sensation and neurogenic inflammatory responses, and secondary infection (Jameson, 2006).

Last, the nonvascular complications of diabetes mellitus include gastroparesis, which is delayed gastric emptying due to autonomic neuropathy, and it is manifested with nausea, vomiting, and abdominal discomfort, in addition to weight loss, and multiple episodes of hypoglycemia (Fonseca, 2006; Jameson, 2006). Other nonvascular diabetic complications include infections and skin changes (Fonseca, 2006; Jameson, 2006). It is important to note that hyperglycemia resulting from poor diabetic control in both type 1 and type 2 DM patients contributes to the development of microvascular, macrovascular, and nonvascular complications (Fonseca, 2006; Jameson, 2006).
According to the DCCT trial, good glycemic control with HgA1C less than 7 will prevent or postpone diabetic complications, in particular the microvascular complications (DCCT, 1993). This can be achieved by the administration of multiple daily insulin injections (MDI) or a continuous subcutaneous insulin infusion via a pump (CSII). The MDI treatment requires the use of multiple insulin injections, such as long-acting insulin analogues, Lantus or levemir, and rapid acting analogues, such as Humalog, Novolog, or Apidra (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006).

On the other hand, insulin pumps (CSII) are flexible in delivering insulin in that they allow for adjustments in the delivery rate or dose size when necessary (Bruttomesso, Costa, & Baritussio, 2009). Continuous subcutaneous insulin infusion via a pump (CSII) is considered a good way of delivering insulin since it mimics most closely the pattern of insulin secretion by the beta cells in the pancreas (Bruttomesso et al., 2009). Insulin pumps have improved enormously over the years to provide better metabolic control for diabetic patients (Bruttomesso et al., 2009).

The insulin pump is a computerized and automatic device that delivers insulin (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). It is the size of a pager and weighs about four ounces (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). In addition, it can be placed in a pocket, on a belt, inside a sock, or in a special bra (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). Continuous subcutaneous insulin infusion via a pump (CSII) delivers a continuous amount of insulin through an automatic push of a plunger of a large syringe that usually holds up to 3.0 ml or 300 units of insulin (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). The pump delivers a continuous amount of insulin automatically for 24 hours a day, which is considered the insulin basal rate (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). The basal rate of insulin administration can be adjusted with a precision down
to 0.025 units per hour, which allows for an individualized basal rate that matches each patient’s requirements (Fonseca, 2006; American Diabetes Association [ADA], 2003). The pump delivers insulin to match the carbohydrate content of a meal. The insulin bolus profiles used can be chosen to match the carbohydrate content of a meal, the meal composition, and nutrient absorption (Fonseca, 2006; ADA, 2003). Thus, patients can choose square- or extended-wave boluses to cover the mixed meals or to compensate for gastroparesis (Fonseca, 2006; ADA, 2003).

The insulin coming from the syringe in the pump is carried through a long adjustable tube connected to a catheter that is inserted preferably in the patients’ abdominal area (Fonseca, 2006; Wolpert, 2002). Other sites for infusing the catheter include the upper outer quadrant of the buttocks area, the upper thigh area, and the triceps fat pad of the arms area (Fonseca, 2006; Wolpert, 2002). The infusion site of the long tube to the catheter is removable, which allows for the easy release of the tube from the catheter (Fonseca, 2006; Wolpert, 2002). This mechanism comes in handy when the pump patient is showering, swimming, and dressing (Fonseca, 2006; Wolpert, 2002). The syringe and the catheter should be changed every 3 days (Fonseca, 2006; Wolpert, 2002). Problems arising from using the infusion set for more than 3 days include inflammation and abscesses that can hinder the proper delivery of insulin and require further treatment, such as drainage of the abscess and administration of antibiotics (Fonseca, 2006; Wolpert, 2002). The three new models of insulin pumps including Deltec Cosmo, Medtronic Minimed Paradigm, and Animas 1200 have built-in alarms that are activated to warn the patient if the insulin supply is low or the infusion set is occluded. This helps in preventing episodes of hyperglycemia (Fonseca, 2006; Wolpert, 2002).
Some insulin pumps have software programs to calculate bolus and correction doses based on insulin-to-carbohydrate ratios (ADA, 2003). Furthermore, some pump models allow the wireless transmission of blood glucose values from a glucose meter to the pump, and it is now possible to download pump data to draw graphical illustrations of insulin rates, frequency of boluses, type of bolus infusion, and timing of catheter changes (ADA, 2003). This in turn helps the pump patients better control their blood sugars and prevent episodes of hyper- and hypoglycemia. Other pump innovations include sensor-augmented pumps, which are currently under evaluation (ADA, 2003). They combine the features of newer pumps with a real time glucose sensor (ADA, 2003). The glucose sensor allows patients to improve their glycemic control without increasing the amount of time spent in the hypoglycemic range through giving the patient blood glucose readings every 5 minutes (ADA, 2003).

**Statement of the Problem**

Since diabetes results in many metabolic consequences, controlling the blood sugar and slowing the progression of the disease is of a paramount importance. Achieving good glycemic control with HgA1C less than 6.5 can be done with less incidence of hypoglycemia by using multiple daily insulin injections or by delivering insulin via a pump (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). Because of the ease of the use of the pump and the removal of the need of daily injections, the pump has gained more recognition over the multiple daily injections of insulin (MDI) during the last few years. Even though continuous subcutaneous insulin infusion (CSII) has gained recognition, there are not enough data to support the superiority of the use of CSII over the MDI in regard to the overall glycemic control in the majority of type 1 DM patients. At the present time, the CSII therapy is mostly used for type 1 DM patients with recurrent or severe hypoglycemia, patients with wide fluctuations in the blood
glucose levels regardless of the HgA1C levels, and children and adolescents with a pronounced dawn phenomenon, as well as children with needle phobia and pregnant adolescents (ADA, 2003).

**Objective of the Study**

The objective of this study is to compare two groups of type 1 DM patients, one of whom received MDI injections of insulin and the other of whom received insulin infusions via a pump. Information regarding HgA1C, fasting blood sugar, and incidence of hypoglycemia, including the total number of hypoglycemic events, severe hypoglycemia, and nocturnal hypoglycemia within a 6-month period, was collected. In addition, the number of incidents of diabetic ketoacidosis (DKA) within a 6-month period was recorded. This information was gathered from patients’ charts obtained from St. Bernardino Endocrine Clinic located at 399 East Highland Avenue, 4th Floor, Suite 427, San Bernadino, California. Permission was obtained from the director of this clinic to allow collection of these data.

**Significance of the Study**

The study is an unbiased one that evaluated the use of multiple daily injections of insulin (MDI) to the use of insulin pumps (CSII) in patients with type 1 DM in regulating glycemic control, reducing the incidence of symptomatic hypoglycemia and decreasing the incidence of hospitalization related to diabetic ketoacidosis.
CHAPTER 2: REVIEW OF RELATED LITERATURE

The current standard of care for patients with type 1 Diabetes Mellitus includes intensive multiple daily injections of insulin (MDI) or administration of insulin through a medical device referred to as continuous subcutaneous insulin infusion (CSII; ADA, 2003). There are four types of available insulin regimens used with diabetic patients: 1) rapid-acting insulin, such as Novolog, Humalog, and Apidra, with rapid onset of action of 5-15 min, a peak of action of 1-1.5 hrs, and a duration of action of 4 hours; 2) short-acting insulin, such as regular insulin with an onset of action of 30-60 min, a peak of action of 2 hrs, and a duration of action of 6-8 hrs; 3) intermediate-acting insulin, such as Neutral Protamine Hagedorn (NPH) insulin, with an onset of 2-4 hrs, a peak of action of 6-7 hrs, and a duration of 10-20 hrs; and 4) long-acting insulin, such as Lantus and Levemir, with an onset of 1-1.5 hrs, with no peak, and a duration of action of 17-24 hrs (Gardner & Shoback, 2007). These insulin regimens are delivered through different methods in type 1 DM patients. The methods of delivery of insulin include disposable plastic syringes with needles, insulin pens, or continuous subcutaneous insulin infusion via pumps (CSII; Gardner & Shoback, 2007).

The Diabetes Control and Complication trial (DCCT) using NPH and regular insulin indicated that good glycemic control in type 1 DM could be achieved with multiple daily insulin injections (MDI), an intensive insulin therapy, when compared to one or two insulin injections, a conventional insulin therapy. Recently, intensive insulin therapy has been used for type 1DM patients either via multiple daily injections (MDI) or via insulin pumps (CSII; Gardner & Shoback, 2007).

Intensive insulin therapy uses a combination of long acting insulin, such as Lantus and Levemir, and rapid acting insulin, such as Novolog, Humalog, and Apidra, with patients on
multiple daily injections (MDI; Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006). In addition, it uses rapid acting insulin, such as Novolog, Humalog, or Apidra, which is delivered continuously with patients on insulin pumps (CSII). Even though both MDI and CSII provide intensive insulin therapy, CSII has gained popularity over the MDI because of the ease of use without the use of daily injections (Gardner & Shoback, 2007; Fonseca, 2006; Jameson, 2006).

This insulin pump (CSII) is considered a good way to deliver insulin since it mimics most closely the pattern of insulin secretion by the beta cells in the pancreas (Bruttomesso, Costa, & Baritussio, 2009). In addition, insulin pumps have improved enormously over the years to provide better metabolic control (Bruttomesso et al., 2009). Optimal metabolic control is important to reduce the risk of the longterm micro-complications in type 1 DM patients (DCCT, 1993). Even though the use of CSII may contribute to better glycemic control and decrease the risk for micro-complications, it should not be used with some groups of patients (Bruttomesso et al., 2009). The groups of patients who are contraindicated for the use of the insulin pump include patients with a history of poor compliance, unwillingness or inability to calculate meal doses, and unwillingness to carry out at least 4 blood glucose tests daily, in addition to patients with evidence of psychiatric conditions, such as severe recurrent or unresolved depression, history of suicide attempts, and severe eating disorders (Bruttomesso et al., 2009). Blindness and deafness are not absolute contraindications to the use of insulin pumps (Bruttomesso et al., 2009). Retinopathy requiring laser therapy could be a temporary contraindication to the use of insulin pump therapy because starting CSII when having this condition may contribute to retinopathy deterioration, especially if the patient’s values of hemoglobin HgA1C are very high (Bruttomesso et al., 2009). As a result, it is advisable to laser-treat retinopathy before starting the insulin pump (Bruttomesso et al., 2009). Available evidence indicates that unfavorable events
during insulin pump use occur mostly in poorly selected type 1 DM patients, when the caring team is not well coordinated or inadequately trained in regard to insulin pump use (Bruttomesso et al., 2009).

Confounding evidence exists on the effect of the CSII use in lowering HgA1C levels, an indicator of blood sugar control during the previous 2- to 3-month period, when compared with the use of MDI in type 1 DM patients (Gardner & Shoback, 2007). A study included that patients with a mean age of 12 years showed an overall small but significant improvement of HgA1C levels from 8.1 to 7.7 with the use of CSII therapy (PlontNich, Loretta, Frederick, & Thomas, 2003). Another study conducted on patients with mean age of 13.8 ± 6.1 at the initiation of the pump therapy demonstrated that the initiation of CSII in children with high HgA1C level reduced their HgA1C concentrations significantly from 9.4 to 8 and stayed stable thereafter (Pinhas-Hamiel, Tzadok, Hirsh, Boyko, Graph-Barel, Lerner-Geva, & Richman, 2010).

However, HgA1C values in adolescents aged 12-17 years who used either MDI or CSII revealed that patients on CSII with HgA1C of 8.5 did not show a significant decrease in HgA1C levels when compared to adolescents on MDI with HgA1C of 8.2 (Wua, Graves, Roberts, & Mitchell, 2010).

Furthermore, adult type 1 DM patients with mean age of 44 were not able to achieve a desirable HgA1C goal level of less than 7.5 on CSII therapy, as advised by Diabetes Control and Complications trial (Everett, Bowes, & Kerr, 2010). The reason for this difficulty for achieving this desirable level was attributed to patients’ fear of experiencing hypoglycemia when using the pump (Everett et al., 2010). The patients’ fear was due to lacking the needed education that enabled patients to adjust the pump settings, especially the setting concerning the basal insulin
rates. This lack of education hindered patients from using available pump settings to achieve HgA1C level less than 7.5 (Everett et al., 2010).

The Diabetes Control and Complication Trial (DCCT) indicated that patients using CSII had lower HgA1C values than patients on MDI (DCCT, 1993). A meta-analysis study including 12 randomized studies that compared MDI and CSII adult patients revealed that the use of CSII caused a decrease in the blood glucose levels and HgA1C levels more than the MDI group. The mean difference of the blood glucose concentrations between both groups was 1 mmol/L, and the difference in HgA1C values between both groups was 0.51% (Pickup, Martin, & Kerry, 2002). This study concluded that the blood glucose control is better with the use of CSII therapy than MDI therapy (Pickup et al., 2002).

Even though a decrease in HgA1C values in type 1 DM patients with the use of CSII when compared to MDI exists, perplexing evidence is found as it relates to the decrease in the HgA1C levels and the ability to reach the advisable level of less than 6.5 of HgA1C, as advised by the American Endocrine Society with the use of CSII in different age groups (Plontnich et al., 2003). As a result, further investigation is needed as it relates to the effect of CSII on the blood sugar concentrations and HgA1C values in type 1 diabetic patients when compared to MDI (Plontnich et al., 2003).

On the other hand, studies comparing the total incidence of hypoglycemia, a blood glucose value of less than 70 mg/dl, between patients on MDI and CSII showed that patients on CSII have fewer events of hypoglycemia than those on MDI (Gardner & Shoback, 2007; Plontnich et al., 2003; Karagianni, Sampanis, Katsoulis, Miserlis, Polyzos, Zografou, Stergiopoulos, Douloumbakis, & Zamboulis, 2009; Kordonouri, Hartmann, & Danne, 2011). Karagianni et al. compared two groups of type 1 diabetic patients aged 30 to 32 years. One group
used MDI therapy and the other group used CSII therapy (Karagianni et al., 2009). Each group included 17 patients, who were matched for age, BMI, gender, and the duration for diabetes (Karagianni et al., 2009). The two groups were retrospectively compared for a period of 6 months regarding the number of hypoglycemic episodes and HgA1C (Karagianni et al., 2009). After 6 months of the initiation of the study, the CSII group reported fewer hypoglycemic incidences per month (8.7) and HgA1C value of (7.3) than the MDI group, which showed increased frequency and severity of hypoglycemic incidences per month with a mean value of (10.8) and HgA1C value of (7.9; Karagianni et al., 2009).

Evidence obtained from multiple trials had shown that patients on insulin pumps have fewer episodes of severe hypoglycemia (Gardner & Shoback, 2007; Bruttomesso et al., 2009; Pickup & Sutton, 2008). A meta-analysis of 22 studies was conducted to compare the incidences of severe hypoglycemia and the glycemic control in using MDI and CSII therapies (Pickup & Sutton, 2008). It was noted that severe hypoglycemia was reduced in type 1 DM patients using CSII therapy when compared to MDI therapy (Pickup & Sutton, 2008). The MDI group showed a total number of severe hypoglycemic events of 62 events/100 patients, whereas the total number of severe hypoglycemic events in the CSII group was 14.8 events/100 patients (Pickup & Sutton, 2008). Controlling blood sugar via an insulin pump increases awareness of hypoglycemia and improves the activity of counter regulatory hormones, which in turn contributes to a decrease in the incidence of hypoglycemia (Pickup & Sutton, 2008). Another study compared the incidences of severe hypoglycemia between MDI and CSII therapy (Boland, Grey, Oestrerle, Fredrickson, & Tamborlane, 1999). The study included 75 patients, including 50 on MDI and 25 on CSII, who switched from MDI at the beginning of the study (Boland et al., 1999). The patients were 12-20 years old. Parameters compared between the two groups
included severe hypoglycemic incidences and HgA1C levels in a 12-month period (Boland et al., 1999). The MDI group showed an increase in HgA1C levels from 8.1 in the beginning of the study to 8.3 at the end of the study (Boland et al., 1999). However, the CSII group showed a decrease in HgA1C levels from 7.7 in the beginning of the study to 7.5 at the end of the study (Boland et al., 1999). The decrease in the HgA1C values was in favor of the CSII group and was accompanied by a significant 50% reduction of severe hypoglycemic incidences in favor of the CSII group (P=0.01) (Boland et al., 1999). The number of severe hypoglycemic incidences in the MDI group was 134 incidences, and the number of severe hypoglycemic incidences in the CSII group was 76 incidences (Boland et al., 1999).

Continuous subcutaneous insulin infusion (CSII) use in type 1 DM patients may decrease the incidence of hypoglycemia, including total number of hypoglycemic incidences and severe hypoglycemia when compared to MDI (Wua et al., 2010). However, more data are needed to prove the superiority of using CSII therapy over the MDI therapy in regard to lower incidence of hypoglycemia (Pickup & Sutton, 2008).

Diabetes Ketoacidosis is a state of uncontrolled catabolism triggered by a relative or absolute deficiency in the circulating insulin; it includes a triad of high anion gap metabolic acidosis (pH less than 7.35), hyperglycemia (blood glucose levels more than 250 mg/dl), and positive ketones in the blood or urine (Gardner & Shoback, 2007; Fonseca, 2006). In experienced diabetic centers, the incidence of DKA is lower with patients using insulin pumps than in patients using MDI injections (Gardner & Shoback, 2007; Bruttomesso et al., 2009; Doyle, Weinzimer, Steffen, Ahern, Vincent, & Tamborlane, 2004). Previous older studies report a high rate of diabetic ketoacidosis (DKA) with the use of CSII (Gardner & Shoback, 2007; Fonseca, 2006). The incidence of DKA in CSII patients is attributed to malfunction of the
infusion system or inflammation of the infusion site (Bruttomesso et al., 2009). The malfunction of the infusion system can be attributed to depletion of the insulin depot (Bruttomesso et al., 2009). As a result, insulinopenia, which is insulin deficiency, develops due to stopping the insulin infusion when the small insulin subcutaneous depot is depleted (Guilhem, Leguerrier, Lecordier, Poirier, & Maugendre, 2006). This is evident, especially with the use of quick-acting insulin analogs (Guilhem et al., 2006). In addition, erythema, redness around the infusion site, subcutaneous nodules, or abscesses can develop at the infusion site due to the subcutaneous port infusion, which hinders the insulin infusion and contributes to CSII malfunction and the subsequent development of DKA (Bruttomesso et al., 2009; Guilhem et al., 2006). On the other hand, most recent studies have shown that the use of insulin pumps may decrease the incidence of DKA in patients when compared to MDI (ADA, 2003; Kordonouri et al., 2011). None of the last 15 studies published on this subject in the past 6 years reported a significant increase in the incidence of DKA during insulin pump usage (Plontnich, 2003). Three of them reported a significant reduction in DKA, and three did not report significant changes (Plontnich, 2003). Recurrent illness was the cause of DKA in most of the remaining cases (Plontnich, 2003). To prevent the incidence of diabetic ketoacidosis, it is important to have frequent blood glucose monitoring to check the urine ketones, and to react promptly to technical problems or unexplained hyperglycemia (Plontnich, 2003; Guilhem et al., 2006; Bell & Alele, 1997).

Perplexing evidence exists on the effect of CSII use as it relates to DKA when compared to MDI. Some studies show a decreased rate of DKA with the use of CSII. Others did not report any changes in DKA rate with the use of CSII when compared to MDI. Increasing the patient and physician experience with the use of insulin pumps decreased the incidence of DKA. However, it is important to be aware of technical problems that may arise with the use of insulin
pumps, such as problems caused by malfunction of the pump or inflammation caused at the infusion site. Further investigation is needed to determine the effectiveness of the insulin pump in decreasing the DKA rate in type 1 diabetic patients.

There are conflicting results with studies of patients using MDI and CSII as it relates to HgA1C, hypoglycemia, and DKA. Thus, further studies are needed to evaluate the effectiveness of the use of CSII and to demonstrate whether its use results in better diabetes management and care than use of the MDI.
CHAPTER 3: RESEARCH METHODOLOGY

Research Design

The study included a retrospective review of medical charts of 70 patients including males and females with type 1 DM. These patients were either on MDI or CSII for one year or more before the start of the study, were without a glucose monitor, were aged 18-50 years, and were without any evidence of diabetic complications, such as diabetic nephropathy, diabetic retinopathy, cardiovascular disease, peripheral neuropathy, and peripheral vascular disease. Half of those patients (n=35) received multiple daily injections of insulin for more than one year before the first point of data collection (Group 1), and the other half, 35 patients, used continuous subcutaneous insulin infusion for at least one year prior to the first point of data collection (CSII; Group 2). Only patients who used the pump therapy for a minimum of one year were included in Group 2 in order to allow time for adaptation in the use of technology with the pump. Group 1 included patients on multiple daily insulin injections who take basal long-acting insulin, such as Lantus or Levemir once a day, and rapid-acting insulin, such as Novolog or Humalog, as pre-meal insulin. Group 2 included patients on insulin pump who take rapid-acting insulin, such as Novolog or Humalog.

Patients’ charts from St. Bernardine Endocrine Clinic in San Bernardino, California, were selected depending on the inclusion criteria discussed earlier. Permission was obtained from the director of the clinic, and the study was approved by the Human Subjects Review Board at Eastern Michigan University (see Appendix C). The needed information for the study was recorded in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. The data were recorded in an excel spreadsheet. These data included 1) HgA1C values; 2) fasting blood glucose levels (blood glucose levels after an eight hour fast); 3)
the total number of hypoglycemic events; 4) the number of incidences of severe hypoglycemia; 5) the number of incidences of nocturnal hypoglycemia (hypoglycemia during the night); and 6) the number of episodes of diabetic ketoacidosis (DKA). Nocturnal hypoglycemic symptoms were recorded as self-reported by patients. The previous information was gathered for each of the participating patients per 6-month period for both the MDI patients and CSII patients. Data were collected in three time periods in which the progression of MDI and CSII patients were monitored for HgA1C and fasting blood glucose. Initial data were collected at point zero, and subsequent data were recorded 3 months and 6 months later. Thus, three readings during a 6-month period for each patient were recorded for HgA1C and fasting blood glucose. The number of hypoglycemic events, the number of incidences of severe hypoglycemic events, the number of incidences of nocturnal hypoglycemia, and the number of episodes of DKA were recorded at the end of the 6-month period in both groups.

**Statistical Analysis**

SPSS software was used for the statistical analysis. The analysis compared HgA1C concentration and fasting blood sugar concentrations at three stages (baseline, 3 months, and 6 months) for both MDI and CSII patients by the use of two-sample t-tests of hypothesis for independent samples to compare the different parameters for both populations. In addition, t-tests were used for comparing the number of hypoglycemic events, the number of incidences of severe hypoglycemia, and the number of incidences of nocturnal hypoglycemia for both the MDI and the CSII patients. Furthermore, t-test was used to compare the number of DKA events per 6-month period between the MDI and the pump groups. A P value of 0.05 or less was used to determine the significance between the MDI and the pump means for each stage of the study.
CHAPTER 4: RESULTS

In this study, Group 1 included patients on MDI, and Group 2 included patients on CSII. The sample sizes (n= 35 in each group) in both groups were large enough to provide meaningful results. In the MDI group, 23 patients were females and 12 were males. The CSII group included 20 female patients and 15 male patients. The demographics of both groups were thus comparable. Results were compared using the Two-Sample t-Tests for Independent Samples. SPSS was used for data analysis.

First, HgA1C concentrations in both groups were compared at three stages, including at baseline, 3 months, and 6 months. Mean values for HgA1C are shown in Table 1 and Figure 1. There were no significant differences in the initial HgA1C concentrations between patients who were on MDI (7.61) or on CSII therapy (7.57). At 3 months, HgA1C was lowered in MDI patients (7.46) when compared to their own baseline (7.61) values. Likewise, compared to their own initial (7.58) values, HgA1C concentrations at 3 months (7.19) also declined in patients using the pump. At 6 months, HgA1C concentrations were further lowered in both groups of patients.

An independent sample t-test was used to compare HgA1C concentrations between both groups. At baseline, HgA1C concentrations in both groups were symmetric, and there was no evidence of any sizeable outliers. While initial HgA1C concentrations were thus similar in both groups of patients, at 3 months mean HgA1C values (7.19) in pump patients were significantly lower (p-value =0.005) than values (7.46) in patients using multiple daily injections. Similarly, at 6 months, HgA1C was significantly different (p-value =0.010) between pump (7.04) and MDI (7.25) patients. Thus, these results indicate that the pump patients exhibited slightly better HgA1C values at 3- and 6-month periods than the MDI patients.
Table 1

HgA1C concentrations (mean ± SEM for 35 patients per group) at baseline, 3 months, and 6 months in type 1 diabetic patients using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident at 3 and 6 months (*p-value < 0.010, **p-value < 0.005).

<table>
<thead>
<tr>
<th></th>
<th>MDI</th>
<th>CSII</th>
</tr>
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<tbody>
<tr>
<td>Base line</td>
<td>7.6143±.084</td>
<td>7.5771±.098</td>
</tr>
<tr>
<td>3 months</td>
<td>7.4571±.061</td>
<td>7.1914±.067**</td>
</tr>
<tr>
<td>6 months</td>
<td>7.2457±.055</td>
<td>7.0400±.055*</td>
</tr>
</tbody>
</table>

Figure 1. Bar graph showing HgA1C at baseline, 3 months, and 6 months in type 1 diabetic patients using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. Results are mean ± SEM. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident at 3 and 6 months (**p-value < 0.005, *p-value < 0.010). While there were no significant differences at baseline, at 3 months and at 6 months, values for the CSII group were significantly lower than those in the MDI group. (**p-value<0.005 *p-value <0.010).
Second, fasting blood sugar concentrations were compared at three stages, including at baseline, 3 months, and 6 months. Mean values for fasting blood sugar concentrations are shown in Table 2 and Figure 2. There was no significant difference in the initial means of the fasting blood glucose concentrations between patients who were on MDI (139.34 mg/dl) or on CSII therapy (132 mg/dl). At 3 months fasting, blood glucose values were lowered in MDI patients (127.51 mg/dl) when compared to their baseline (139.34 mg/dl) values. Likewise, fasting blood sugar concentrations at 3 months (123.69 mg/dl) were also lowered using the pump. At 6 months, fasting blood sugar concentrations were further decreased in both groups of patients showing a 122.43 mg/dl value for the MDI patients and 107.51 mg/dl value for the CSII patients.

An independent sample t-test was used to compare fasting blood glucose concentrations between both groups. At baseline, fasting blood glucose concentrations in both groups were symmetric, with no evidence of any sizeable outliers. Furthermore, at the 3-month period, fasting blood glucose concentrations were not significantly different in both groups of patients. However, at 6 months, the fasting blood glucose mean values (107.51 mg/dl) in pump patients were significantly lower (p-value = 0.001) than values (122.43 mg/dl) in patients using multiple daily injections. Thus, these results indicate that CSII patients exhibited significantly better fasting blood glucose values at 6-month periods than did the MDI patients.
Table 2

Fasting blood sugar concentrations (mean ± SEM for 35 patients per group) at baseline, 3 months, and 6 months in type 1 diabetic patients using multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) therapy. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident at 6 months (*p-value < 0.001).

<table>
<thead>
<tr>
<th>Fasting Blood Sugar</th>
<th>MDI (mg/dl)</th>
<th>CSII (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base line</td>
<td>139.34±4.196</td>
<td>132.00±4.811</td>
</tr>
<tr>
<td>3 months</td>
<td>127.51±2.900</td>
<td>123.69±3.330</td>
</tr>
<tr>
<td>6 months</td>
<td>122.43±2.784</td>
<td>104.51±3.224*</td>
</tr>
</tbody>
</table>

Figure 2. Bar graph showing fasting blood sugar at baseline, 3 months, and 6 months in type 1 diabetic patients using multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) therapy. Results are mean ± SEM. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point were evident at 6 months (*p-value < 0.001).
Third, total number of hypoglycemic events, severe hypoglycemic events, and nocturnal hypoglycemia were compared for a 6-month period. Mean values for the previous parameters’ concentrations are shown in Table 3 and Figures 3, 4, and 5. There were significant differences in the mean values of the total number of incidences of hypoglycemia and the nocturnal hypoglycemia in 6 months between the MDI and CSII groups. The mean values of the total number of incidences of hypoglycemia in 6 months were (84.71) in the MDI group and (42.91) in the CSII group. Likewise, a significant difference between mean values of the number of incidences of nocturnal hypoglycemia was evident in the 6-month period between patients on MDI (11.77) and patients on CSII (5.57). On the other hand, there were no significant differences in the mean values of severe hypoglycemic events in a 6-month period between MDI patients (0.23) and CSII patients (0.09). The number of patients experiencing severe hypoglycemia in 6 months in the MDI group was eight, whereas only three patients in the CSII group experienced severe hypoglycemia.

An independent sample t-test was used to compare the total number of hypoglycemic events, the number of severe hypoglycemic events, and the number of nocturnal hypoglycemic events between both groups. For the total number of hypoglycemic events in a 6-month period, the data in both groups were relatively symmetric and consistent with approximate normality. There were sizable outliers at 144 in the MDI group and at 96 in the CSII group, although these outliers were not extreme. The total number of hypoglycemic events in a 6-month period was significantly lower in the CSII group when compared with the MDI group (p-value 0.001). For the total number of nocturnal hypoglycemia in 6 months, data in both groups were symmetric and consistent with approximate normality with no evidence of any sizable outliers. Furthermore, the number of nocturnal hypoglycemic events in 6-month periods was significantly
lower in the CSII group than in the MDI group (p-value 0.001). Data were relatively symmetric for the number of severe hypoglycemic events in 6 months, and thus consistent with approximate normality with no evidence of any sizable outliers. However, there were no significant differences between the two groups. Thus, results showed a significant improvement in the total number of hypoglycemic events and the number of nocturnal hypoglycemic events in a 6-month period in CSII patients compared with MDI patients but not in the number of severe hypoglycemic events.

Table 3

*Total number of hypoglycemic events, the number of severe hypoglycemic events, and the number of nocturnal hypoglycemic events (mean ± SEM for 35 patients per group) during a 6-month period for type 1 diabetic patients using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident in 6 months for the total number of hypoglycemia and the total number of nocturnal hypoglycemia (**p-value < 0.001).*

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>The total # hypoglycemic events /6months*</th>
<th>The # of severe hypoglycemic events /6months</th>
<th>The # of nocturnal hypoglycemic events /6months **</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>84.71±4.24**</td>
<td>0.23±0.07</td>
<td>11.77±1.09**</td>
</tr>
<tr>
<td>CSII</td>
<td>42.91±3.06</td>
<td>0.09±0.05</td>
<td>5.57±0.83</td>
</tr>
</tbody>
</table>
Figure 3. Bar graph showing the total number of hypoglycemic events in 6 months in type 1 diabetic patients using multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) therapy. Results are mean ± SEM. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident in 6 months (p-value< 0.001).

Figure 4. Bar graph showing the total number of severe hypoglycemic events in 6 months in type 1 diabetic patients using multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) therapy. Results are mean ± SEM. No significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident in 6 months (p-value< 0.104).
Figure 5. Bar graph showing the total number of nocturnal hypoglycemic events in 6 months in type 1 diabetic patients using multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) therapy. Results are mean ± SEM. Significant differences by independent-sample t-test, between MDI and CSII patients at the same time point, were evident in 6 months (p-value< 0.001).

Last, diabetes keto-acidosis (DKA) concentrations in both groups were compared in a 6-month period. Mean values for DKA are shown in Table 4 and Figure 6. In a 6-month period, DKA episodes were significantly lower in CSII patients (0.06) than in MDI patients (0.11).

An independent sample t-test was used to compare DKA episodes between both groups. In 6 months, DKA episodes in both groups were symmetric, and there was no evidence of any sizeable outliers. At 6 months, mean DKA values (0.06) in pump patients were not significantly lower than values (0.11) in patients using multiple daily injections. The total number of DKA episodes in MDI patients in a 6-month period was four, whereas the total number of DKA episodes in CSII patients in a 6-month period was two. No significant differences between the MDI and the CSII patients were noted between the two groups.
Table 4

The number of DKA episodes (mean ± SEM for 35 patients per group) in 6 months in type 1 diabetic patients using multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) therapy. There were no significant differences by independent-sample t-test between MDI and CSII patients.

<table>
<thead>
<tr>
<th>Treatment Method</th>
<th>The # DKA episodes /6months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI</td>
<td>.11± 0.04</td>
</tr>
<tr>
<td>CSII</td>
<td>.06± 0.06</td>
</tr>
</tbody>
</table>

Figure 6. Bar graph showing the number of DKA episodes in 6 months in type 1 diabetic patients using multiple daily injections (MDI) or on continuous subcutaneous insulin infusion (CSII) therapy. Results are mean ± SEM. No significant differences by independent-sample t-test between MDI and CSII patients at the same time point were evident in 6 months.
CHAPTER 5: DISCUSSION, RECOMMENDATIONS FOR FURTHER RESEARCH, AND CONCLUSIONS

Discussion

This study represents a retrospective comparison of two groups of type 1 Diabetes Mellitus patients: one who received multiple daily injections of insulin (MDI) and the other who were on insulin pumps (CSII). It evaluated the effectiveness of the use of the insulin pump in regulating blood glucose in these patients. Type 1 DM patients on MDI or CSII were compared by measuring HgA1C, fasting blood glucose, hypoglycemia including incidences of total, severe, and nocturnal hypoglycemia, and Diabetes Ketoacidosis (DKA), which are well known markers for glycemic and metabolic regulation in diabetics.

From the analysis described earlier, it was evident that HgA1C concentrations were reduced in the participants using the pump therapy when compared with the MDI therapy. Glycated hemoglobin or HgA1C is a marker for average blood glucose values over the previous 3 months. The mean HgA1C value for patients using CSII therapy was significantly lower (7.1 and 7 at 3 and 6 months, respectively) than patients treated with MDI (7.4 and 7.2 at 3 and 6 months, respectively). In addition, fasting blood sugar mean levels were lower in patients treated with the pump (107.51mg/dl) than in patients on MDI (122.43mg/dl) at the 6-month period. The decrease in the HgA1C values in this study was similar to other studies with adolescent and adult type 1 DM patients with an age range of 18-50 years old as included in this study. A study with 13.8 ± 6.1 year old type 1 diabetic patients revealed that pump therapy in patients with high HgA1C levels reduced levels significantly from 9.4 to 8 (Pinhas-Hamiel et al., 2010).

Furthermore, the present results also support the results of a meta-analysis study that showed a decrease in the mean blood glucose and HgA1C values of patients using CSII therapy when
compared to MDI therapy (Pickup et al., 2002). On the other hand, results of a study in adult patients with a mean age of 44 on CSII showed that HgA1C level of less than 7.5 was not achieved with CSII therapy (Everett, Bowes, & Kerr, 2010). These results contradicted the results of this study that showed a decrease in HgA1C levels with CSII therapy to a level of ~ 7 after the 6-month period.

Patients on insulin pumps had significantly fewer numbers of total incidences of hypoglycemia and nocturnal hypoglycemia than MDI patients. However, the number of severe hypoglycemic events between the two groups was not significantly different.

There was a decrease in the total number of hypoglycemic events in this study (defined as a blood glucose value of less than 70 mg/dl). These results concur with previous studies that showed a decrease in the total number of incidences of hypoglycemia with the use of the pump therapy (Gardner & Shoback, 2007; Plontnich et al., 2003; Karagianni et al., 2009; Kordonouri et al., 2011). A study done with adult patients 30-32 years old demonstrated that using the insulin pump therapy with type 1 DM patients reduced the number of hypoglycemic incidences to 8.7 per month and their HgA1C values to 7.3 when compared to MDI patients, who showed higher numbers of hypoglycemic incidences per month (10.8) and HgA1c value of (7.9; Karagianni et al., 2009).

There was no significant difference in the number of severe hypoglycemic incidences between the two groups of patients in this study. Results from this study did not correspond to those from other studies that show decreases in the incidences of severe hypoglycemia with the use of CSII therapy (P=0.01; Boland, Grey, Oestrerle, Fredrickson, &Tamborlane, 1999; Pickup & Sutton, 2008). Overall, there were very few incidences of severe hypoglycemia observed. The number of MDI patients displayed eight incidences of severe hypoglycemia, while the CSII
patients showed only three incidences of severe hypoglycemia. It is noteworthy that even though this difference was not statistically significant, there was approximately a 50% decrease in the incidences of severe hypoglycemia in the CSII group. The results of a previous study concurred with this study in that a decrease in the HgA1C levels with the use of CSII in a 12-month period was evident from 7.7 to 7.5 along with a decrease in the incidence of severe hypoglycemic incidences in the CSII group from 134 in the MDI group to 76 in a 12-month period (Boland et al., 2008). The reduction in the occurrence of hypoglycemic incidences between the two groups was almost 50% (Boland et al., 2008) as shown in the current study.

Incidences of nocturnal hypoglycemia (hypoglycemia during the night) were decreased with the use of the pump therapy. The number of nocturnal hypoglycemic incidences was self-reported by the patients in both groups and documented in the patients’ charts. This included the number of times the patients were awakened during their sleep due to hypoglycemic symptoms. The total numbers of nocturnal hypoglycemic incidences for all patients per 6-month period in the MDI group were 11.77 incidences, and the numbers of nocturnal hypoglycemic incidences in the CSII group were 5.57 incidences. Most previous studies did not evaluate nocturnal hypoglycemic incidences in type 1 diabetic patients. The limited number of studies on the effect of CSII use on nocturnal hypoglycemia used a blood glucose monitor with the pump, which was not used in this study.

Diabetes Ketoacidosis is a state of uncontrolled catabolism triggered by a relative or absolute deficiency in the circulating insulin; it includes a triad of high anion gap metabolic acidosis (ph less than 7.35), hyperglycemia (blood glucose levels more than 250 mg/dl), and positive ketones in the blood or urine (Gardner & Shoback, 2007). Since DKA is a life-threatening state with a mortality rate of 5% in patients under the age of 40, it is important to
measure the number of DKA incidences in patients with diabetes (Malone et al., 2001). Higher mortality rate may be noted with DKA incidences in type 1 DM elderly patients (Frank, 1991). Even though a lower incidence of DKA existed in patients with the pump therapy, it was not significantly different between the MDI and the CSII groups. Some previous studies done on patients on MDI and CSII showed a significant decrease in the number of incidences of DKA with the use of the pump therapy (Gardner & Shoback, 2007; Bruttomesso et al., 2009; Doyle et al., 2004). However, the current study supported another study that showed no significant changes between the MDI and the CSII groups (Plontnich et al., 2003). In addition, these results do not correspond with previous older studies that reported a higher number of diabetic ketoacidosis with the use of insulin pumps (Gardner & Shoback, 2007; Fonseca, 2006). This high number was attributed to the malfunction of the infusion system or inflammation of the infusion site (Bruttomesso et al., 2009). It thus seems that when the pump is functioning well, there are no detrimental effects on DKA in CSII patients when compared to MDI patients.

**Recommendations for Further Research**

Further studies are needed to determine the efficacy of the pump use in type 1 DM patients. Research should concentrate on the efficacy of the sensor augmented pump therapy in addition to carbohydrate counting and meal planning and their effect on HgA1C, fasting blood glucose, and hypoglycemic incidences, in addition to the number of severe hypoglycemia, nocturnal hypoglycemia awareness, and diabetes keto-acidosis.

**Conclusions**

The results of this study demonstrated that implementation of insulin pump treatment compared with MDI in selected patients with type 1 diabetes mellitus achieved a significant improvement in HgA1C, blood glucose (glycemic control), and reduced the frequency of overall
hypoglycemic episodes and nocturnal hypoglycemia, but did not impact severe hypoglycemia and diabetes ketoacidosis compared to patients on MDI. Even though a mean level of HgA1C less than 6.5, as advised by the American Clinical Endocrine Society (ACE), or less than 7, as advised by the American Diabetes Association (ADA), was not reached in both groups of patients, the CSII group showed a higher number of individual patients with HgA1C values of less than 6.5 and less than 7 in the MDI group. Six out of 35 MDI patients reduced their HgA1C values to less than 7, and ten out of 35 patients in the CSII group had HgA1C values of less than 7. In addition, no patients on MDI were able to reach a HgA1C values of less than 6.5, and 2 patients out of 35 were able to achieve this value on CSII therapy. Thus, even though the mean HgA1C values in the CSII group did not reach the levels advised by the ADA and ACE, more individual patients with the use of the pump therapy were able to reach these advisable levels.

Further studies are needed to show that treatment with insulin pump, especially when it is combined with continuous glucose monitoring in patients with type 1 DM, can achieve a higher number of patients with HgA1C values than 6.5 with less incidence of hypoglycemic episodes and fewer episodes of diabetes keto-acidosis. In addition, more studies are needed to show the effect of combining life style dietary changes, including carbohydrate counting, meal planning, and diabetes education in conjunction with pump therapy and the continuous glucose monitor on the previously studied parameters in type 1 DM patients.
REFERENCES


APPENDICES
Appendix A: Definition of Terms

Definition of terms

*Dawn phenomenon:* It is a phenomenon seen with 75% of the patients with Type 1 DM, in the majority of patients with type 2 DM, and normal subjects in which there is a reduced sensitivity to insulin between 5am and 8am due to spikes in the growth hormone released hours before and at onset of sleep (1).

*Insulinopenia:* It is insulin deficiency (1).

*Hypoglycemia:* It is a blood glucose value of less than 70 gm/dl (1).

*Diabetic Ketoacidosis (DKA):* It is a state of uncontrolled catabolism triggered by a relative or absolute deficiency in the circulating insulin; it includes a triad of high anion gap metabolic acidosis (ph less than 7.35), hyperglycemia (blood glucose levels more than 250 mg/dl), and positive ketones in the blood or urine (1).

*Neutral Protamine Hagedorn (NPH):* It is an intermediate acting insulin in which the onset of action is delayed by combining two parts of soluble crystalline zinc insulin with one part protamine zinc insulin (1,3). The mixture contains equivalent concentrations of protamine and insulin; its onset of action is delayed to 2-4 hours and its peak response is reached in 6-7 hours; its duration of action is in a range of 10-20 hours (2).

*Regular insulin:* It is short acting insulin analog whose hypoglycemic effect starts after 30-60 minutes after its injection, peaks after 2 hours, and lasts for 6-8 hours (1).

*Lantus and Levamir:* Long acting human insulin analogs that last for 24 hours without showing any peaks along its duration of action (1).

*Humalog, Novolog, Apida:* It is a rapid acting human insulin analogs whose peak values are reached one hour after its injection (1).
**HgA1C**: It is Glycated hemoglobin, which is an indicator of blood sugar control during the previous 2- to 3-month period (1).

**Severe Hypoglycemia**: It is a blood glucose value of less than 40 gm/dl with neuroglycopenic symptoms, which include reduced intellectual capacity, confusion, irritability, abnormal behavior, convulsions, and coma in which the patient needs a third party for the administration of intramuscular or subcutaneous glucagon or intravenous administration of glucose using 50 percent dextrose solution (D50) (1).

**Multiple Daily Injections of insulin (MDI)**: It is part of the intensive insulin therapy used with Type 1 and some Type 2 diabetes mellitus (DM) patients in which multiple injections of insulin including long acting insulin analogs, such as Lantus or Levemir are combined with rapid acting insulin analogs, such as Novolog, Humalog, or Apidra (1).

**Continuous Subcutaneous Insulin Infusion (CSII)**: It is a therapy that delivers a continuous amount of rapid acting insulin to the blood, such as Novolog, Humalog, or Apidra, which mimics most closely the pattern of insulin secretion by the beta cells in the pancreas via a pump medical devise (6).

**Intensive insulin therapy**: An insulin therapy used for Type 1 and some Type 2 DM patients which includes multiple daily insulin injections regardless of the type of the insulin used (1).

**Conventional insulin therapy**: An insulin therapy used for Type 1 or Type 2 DM patients, which includes one or two injections of insulin per day only (1).
Appendix B: Physician’s Permission Letter

Bashar G. Saad, M.D.
Board Certified in Endocrine, Diabetes, Metabolism and Internal Medicine

To whom it may concern,

I, Bashar Saad, MD, the entrepreneur of St. Bernardine Endocrine Clinic in St. Bernardino, CA give the permission to EMU student, Nadia Nameh-Saad, to perform a retrospective study and access my patients’ charts without the use of a consent form from the patients. The student will record the needed information from the charts in a manner that subjects cannot be identified directly or through identifiers linked to the subjects. This will be done through discarding the list of patients’ names after data collection that corresponds to the number code given to each patient. In addition, no treatment change with the patients will be conducted. As a result, HIPPA regulations will not be violated.

Bashar G Saad, MD

Signature

Phone (909) 882-1210 • Fax (909) 882-0716
399 East Highland Avenue, Fourth Floor, Suite 427 • San Bernardino, California 92404
Appendix C: Human Subject Approval Letter

Dear Nadia M. Nemeh-Saad,

Congratulations! After careful review, your proposal "Effectiveness of Insulin Pump use in Controlling Blood Glucose in Type 1 Diabetes Mellitus Patients." has been accepted by the College of Health and Human Services Human Subjects committee. We stress that you do not stray from your proposed plan.

Good luck with your research effort.

The current version of your paper is available here:

http://commons.emich.edu/cgi/preview.cgi?article=1053&context=chhs_hs

Enjoy your experience. Your study will make important contributions to the health field.

Sincerely,

Gretchen Dahl Reeves, Phd.

Chair, CHHS-HS